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PATENT TRADEMARK OFFICE

BENZIMIDAZOLONES AND ANALOGUES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U. S. Patent Application No. 09/552,546, filed April 19, 2000, which claims the benefit of the priority of US Patent Application No. 60/183,036, filed May 4, 1999, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to compounds which are agonists and antagonists of the progesterone receptor, their preparation and utility.

Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus which can lead to an

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increased risk of uterine cancers. Co-administration of a PR agonist reduces/ablates that risk.

PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 July 4, 1996).

PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, Horm. Cancer, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (U.S. Patent No. 5,719,136).

PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N.Y. Acad. Sci.*, ***761, 224, 1995).***

The compounds of this invention have been shown to act as competitive inhibitors of progesterone binding to the PR and act as agonists and/or antagonists in functional models, either/or *in-vitro* and *in-vivo*. These compounds may be used for contraception, in the treatment of fibroids, endometriosis, breast, uterine, ovarian and prostate cancer, and post menopausal hormone replacement therapy.

Jones, *et al,* (U.S. Patent No. 5,688,810) disclose the PR antagonist dihydroquinoline **1**.

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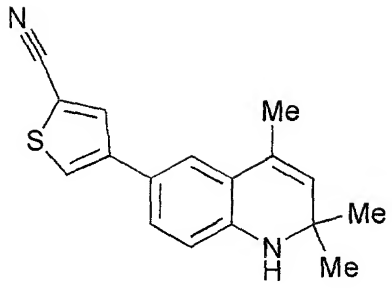
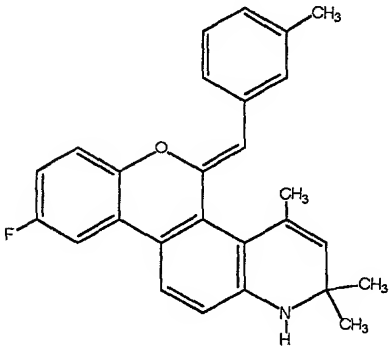


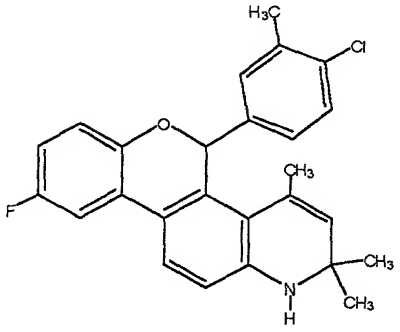
1

Jones, *et al*, described the enol ether **2** (U.S. Patent No. 5,693,646) as a PR ligand.



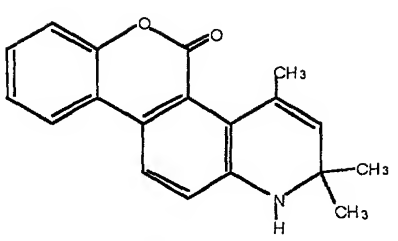
2

Jones, *et al*, described compound **3** (U.S. Patent No. 5,696,127) as a PR ligand.



3

Zhi, *et al*, described lactones **4**, **5** and **6** as PR antagonists (J. Med. Chem., 41, 291, 1998).



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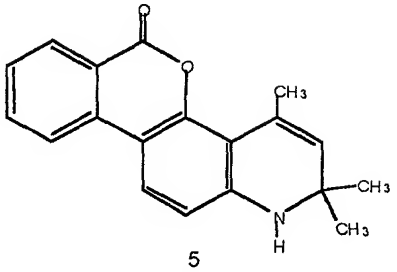

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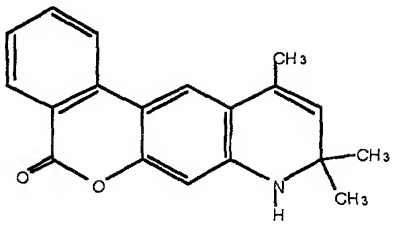
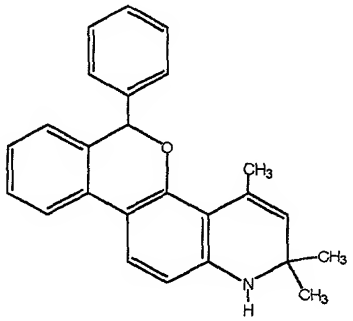


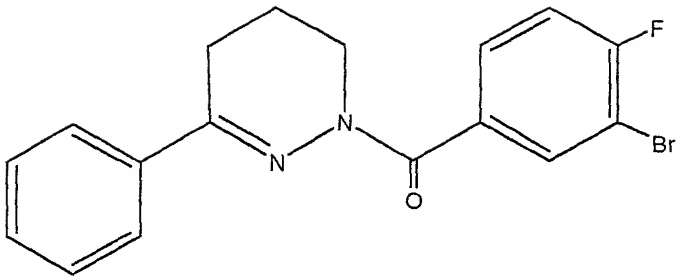
6

Zhi, *et al*, described the ether **7** as a PR antagonist (J. Med. Chem., **41**, 291, 1998).



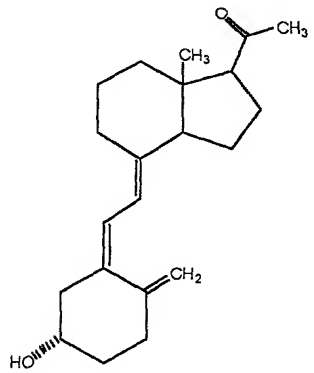
7

Combs, *et al.*, disclosed the amide **8** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



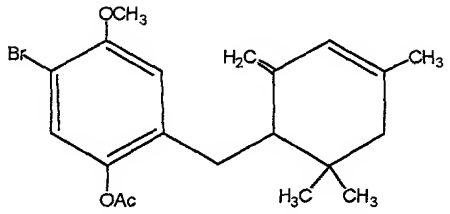
8

Perlman, *et. al.*, described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



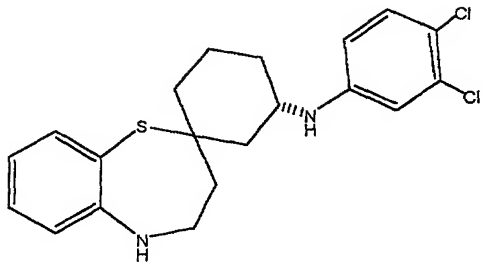
9

Hamann, *et al*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



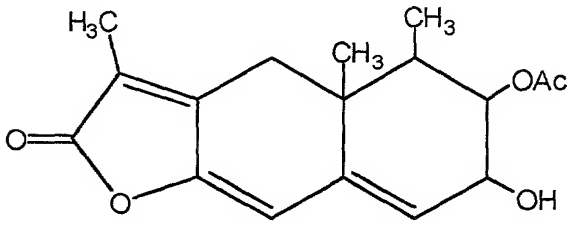
10

Chen, *et al*, described the PR antagonist **11** (Chen, et al, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



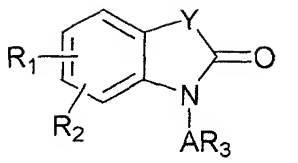
11

Kurihari, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).

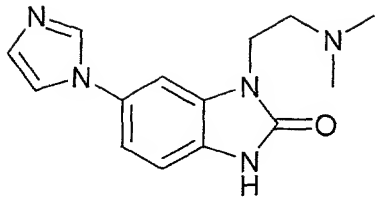


12

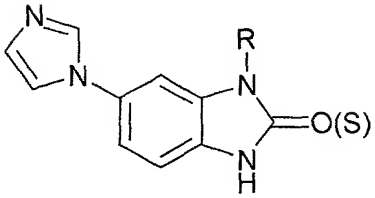
Among the examples of the prior art, Ueda et al. (EP 22317) claimed benzothiazoline and benzoxazoline compounds of formula **A** as the inhibitors of aldose reductase. The benzimidazolinone derivatives such as compound **B** were disclosed by Hara et al. (EP 454330) and claimed as lung surfactant secretion promoters. In their preparation of benzoimidazole and analogues as antiulcer and cardiovascular agents, Bru-Magniez et al. (EP 385850) synthesized the benzoimidazolinones such as compound **C.** Used as cAMP PDE III inhibitors, benzoimidazolinones, benzoxazolinones, and benzothiazolinones as shown in formula **D** were reported by Singh et al (*J. Med. Chem.*, **37**, 248-254 (1994)).



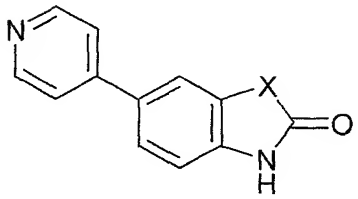
A



B



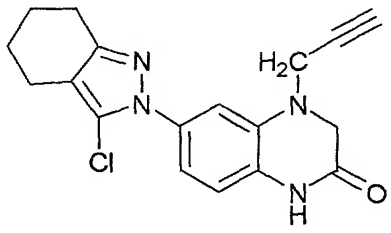
C



D (X = NH, O, S)

The compounds in the present invention contain a pendent aromatic substituent and other substructural features. The aromatic substituents and those substructural features proved to be critical for the resultant compounds being active as progesterone receptor modulators.

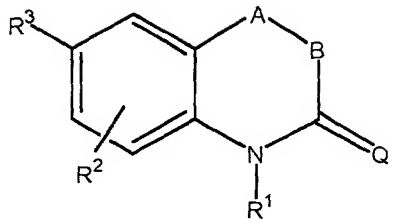
Related to quinoxalin-2-ones, European patent (Ganzer et al. EP 311135) discloses the compounds such as **E** as herbicides.



E

DESCRIPTION OF THE INVENTION

This invention provides compounds of the formula:



wherein:

A is O, S, or NR^4;

B is a bond between A and C=Q, or the moiety CR^5R^6;

R^4, R^5, R^6 are independently selected from H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, cyclic alkyl constructed by fusing R^4 and R^5 to from a 5 to 7 membered ring;

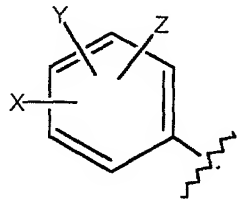
R^1 is selected from H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^A;

R^A is selected from H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^2 is selected from H, halogen, CN, NO_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^3 is selected from a) or b):

a) R^3 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



;

X is selected from the group of halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkoxy, substituted C_1 to C_3 thioalkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^B, $OCOR^B$, or NR^CCOR^B;

R^B is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkoxy;

or

b) R^3 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O S, SO, SO_2 or NR^7 and containing one or two independent substituents from the group of H, halogen, CN, NO_2 and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^D, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^7 is H, or C_1 to C_3 alkyl;

Q is O, S, NR^8, or CR^9R^{10};

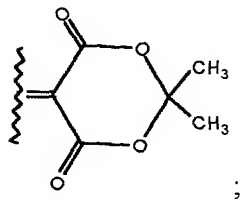
R_8 is selected from the group of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3;

R^9 and R^{10} are independent substituents from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R^{11};

R^{11} is C_1 to C_3 alkyl;

SUBSTITUTE SHEET (RULE 26)

or CR^9R^{10} may comprise a six membered ring of the structure below:



;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of this invention include those of the general formula described above wherein:

A is O, S, or NR^4;

B is a bond between A and C=Q, or the moiety CR^5R^6;

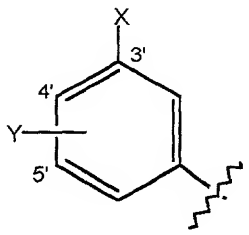
R^4, R^5, R^6 are independent substituents from the group including H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or cyclic alkyl constructed by fusing R^4 and R^5 to from a 5 to 7 membered ring;

R^1 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^A;

R^A is H, C_1 to C_4 alkyl, C_1 to C_4 alkoxy;

R^2 is H, halogen, NO_2, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is a disubstituted benzene ring containing the substituents X and Y as shown below



;

X is taken from the group of halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkoxy;

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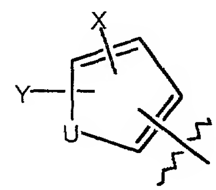
Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkoxy;

or

R^3 is a five membered ring with the structure:



wherein:

U is O, S, or NR^7;

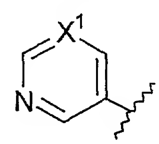
R^7 is H, C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from the group of halogen, CN, NO_2, C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl;

or

R^5 is a six membered ring with the structure:



X^1 is N or CX^2;

X^2 is halogen, CN or NO_2,;

Q is O, S, NR^7, CR^8R^9;

R^8 is from the group of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^9 and R^{10} are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^{10};

R^{11} is C_1 to C_3 alkyl;

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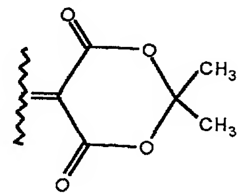
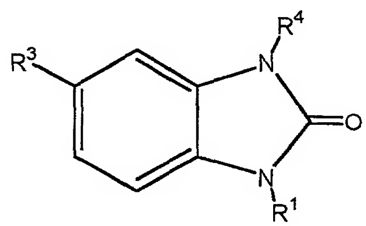
or CR^9R^{10} comprise a six membered ring as shown by the structure:



;

or a pharmaceutically acceptable salt thereof.

Another preferred subgroup of this invention comprises compounds of the general formula:



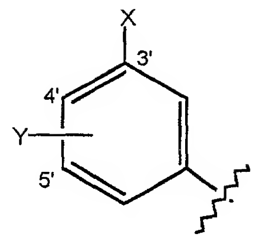
wherein:

R^1 is selected from H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^A;

R^A is selected from H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, benzyl, or substituted benzyl; and

R^3 is selected from halogen or a disubstituted benzene ring containing the substituents X and Y as shown below



;

X is taken from the group of halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, or C_1 to C_3 thioalkoxy;

Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkoxy;

or a pharmaceutically acceptable salt thereof.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, II, and III, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having one to eight carbon atoms, preferably one to six carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond and two to eight carbon atoms, preferably two to six carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond and two to eight carbon atoms, preferably two to six carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO_2, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon

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of an alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

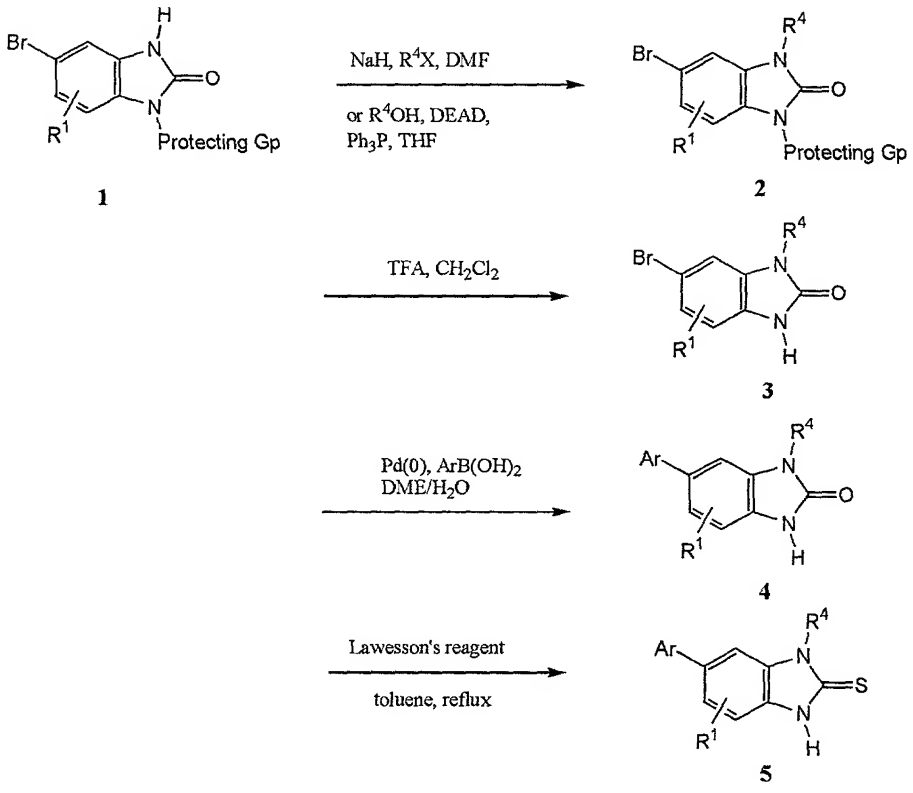
The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but are not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl. The term "substituted aryl" refers to aryl as just defined having one to four substituents from the group including halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl. The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one to four substituents selected from the group which includes halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO

group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups, containing one to eight carbon atoms, which may be either same or different and the point of attachment is on the nitrogen atom. The term "halogen" refers to Cl, Br, F, or I.

The compounds of the present invention can be prepared as described in the following schemes:

Scheme I



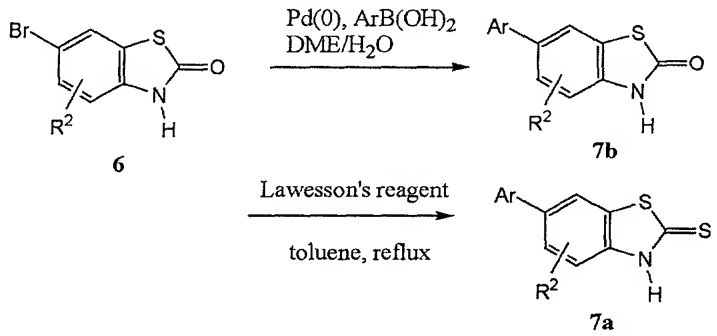
As illustrated in Scheme I, the compounds of this invention are generally prepared by employing the suitable coupling reaction as a final step and further

converted to the thiourea analogues. Thus, appropriately protected benzoimidazolinones **1** (numerous protecting groups including but not limited to alkyloxycarbonyls, such as BOC group, can be employed in the starting material **1**) readily prepared according to the procedure of Meanwell et al. (*J. Org. Chem.* **60**, 1565-1582(1995) can be alkylated at position-3 under a number of conditions. Among the reaction protocols, compound **1** can be alkylated by treatment of **1** with a suitable base such as sodium hydride in an appropriate nonprotic solvent such as DMF followed by addition of an alkylating agent such as alkyl iodide or triflate. Alternatively, the compound **2** can be effected employing a Mitsunobu protocol. The conventional Mitsunobu reaction can couple the compound **1** with an appropriate alcohol using a phosphorous reagent such as triphenyl phosphine and a dehydrating agent such as DEAD (diethyl azodicarboxylate) in a suitable solvent such as THF at temperatures ranging from 0 °C to the boiling point of the solvent employed. Deprotection of compound **2** to give **3** can be furnished *via* numerous conditions, such as acidic deprotection, using an acid such as neat trifluoroacetic acid or basic deprotection employing a base, such as sodium alkoxide in a suitable solvent, such as THF or alcohol at temperature ranging from ambient temperature to the boiling point of the solvent employed. The compounds of this invention, **4**, can be readily prepared by employing various coupling reactions including Suzuki, Stille protocols. These reactions are commonly performed in the presence of transition metallic catalyst, e.g., palladium or nickel complex often with phosphino ligands, e.g., Ph_3P, 1,1'-bis(diphenylphosphino)ferrocene, 1,2-bis(diphenylphosphino)ethane or a catalyst such as palladium acetate. Under this catalytic condition, an appropriately substituted nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, is coupled with bromobenzoimidazolinones **3** to give compounds **4**. An appropriate base is often needed in the reaction; the commonly used bases include but are not limited to sodium bicarbonate, sodium carbonate, potassium phosphate, barium carbonate, cesium fluoride, or potassium acetate. The most commonly used solvents in these reactions include benzene, DMF, isopropanol, ethanol, DME, ether, acetone or a

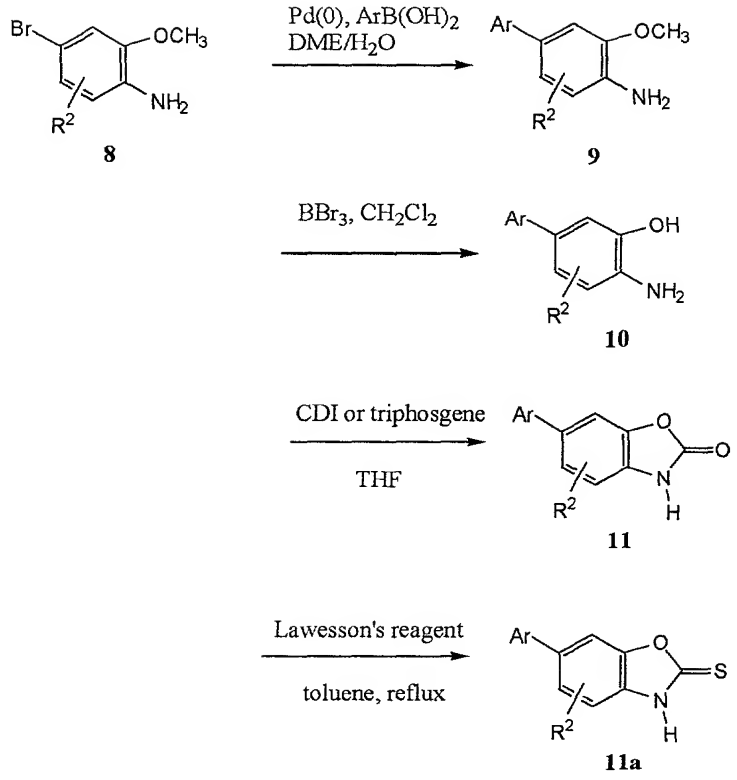
mixture of above solvent and water. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to 95 °C.

The compounds of this invention, **5**, can be easily prepared using an appropriate sulfur reagent such as Lawesson's reagent or P_2S_5 in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

Scheme II



Scheme III



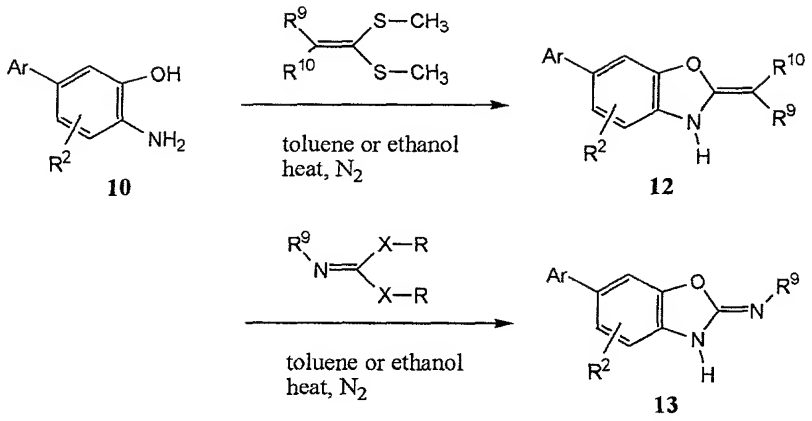
As shown in scheme II, 5-aryl benzothiazolinones **7** can be readily prepared from an appropriate 5-bromo-benzothiazolinone **6** and a suitable electrophile such as an aryl boronic acid, aryl tin reagent, or aryl zinc reagent *via* a suitable coupling reaction as described for the synthesis of benzimidazolinones **4**. Conversion of **7b** into **7a** can be effected using an appropriate sulfur reagent such as Lawesson's reagent or P_2S_5 in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

The synthetic approaches leading to the 5-aryl benzoxazolinones **11** is described in scheme III. As illustrated in scheme III, an appropriately substituted bromo *o*-anisidine can be coupled with an appropriate electrophile such as aryl boronic

acid or aryl tin reagent *via* a coupling reaction as described for the synthesis of compounds **4** to give the biaryl **9**. Demethylation of biaryl **9** to give amino phenol **10** can be accomplished *via* various conditions including treatment of **9** with a strong Lewis acid such as boron tribromide in a suitable solvent such as methylene chloride or treatment of **9** with a mixture of a suitable Lewis acid such as aluminum chloride and a soft nucleophile such as thiol in a suitable solvent such as methylene chloride under an inert atmosphere such as argon or nitrogen. Ring closure of amino phenol **10** to produce the compounds of this invention, **11**, can be effected by using a appropriate condensing agent such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate in a suitable nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C. Conversion of **11** into **11a** can be accomplished using an appropriate sulfur reagent such as Lawesson's reagent or P_2S_5 in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

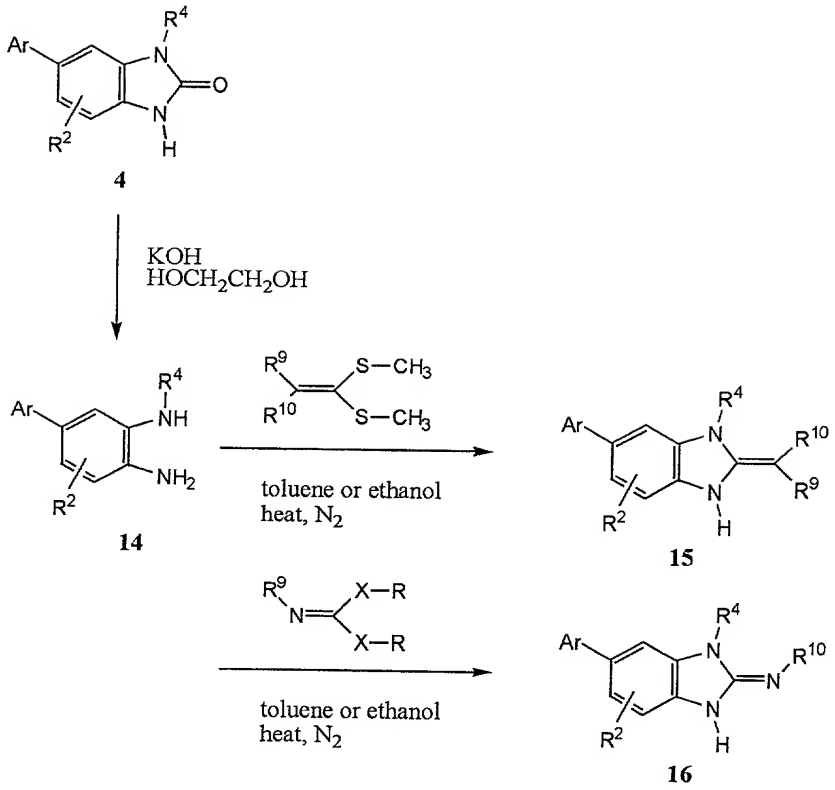
Schemes IV, V, and VI describe the synthesis of other 5-aryl benzoimidazolinone, 5-aryl benzothiazolinone, 5-aryl benzoxazolinone bioisosteres. Using a similar procedure reported by Kondo et al. (Kondo, et al. *J. Med. Chem.* **33(7)**, 2012-2015(1990)) compound **12, 15,** or **18** can be effected by treatment of compound **10**, **14**, or **17** with an appropriate ketene-*S, S*-acetals (at least one of R^9 or R^{10} is an electron withdrawing group) in a suitable solvent such as toluene or anhydrous ethanol under an inert atmosphere such as nitrogen or argon at reflux. In a similar fashion, compounds **13**, **16**, or **19** can be prepared by reaction of compound **10**, **14**, or **17** with appropriate imino-*S, S*-acetals or imino-acetals (R^9 is an electron withdrawing group) employing a procedure similar to that of Evers, et al. (*I. Prakt. Chem.* **333(5)**, 699-710 (1991)) or Haake et al. (*Synthesis-Stuttgart* **9**, 753-758 (1991)) in a suitable solvent such as ethanol under an inert atmosphere such as argon or nitrogen at reflux.

Scheme IV



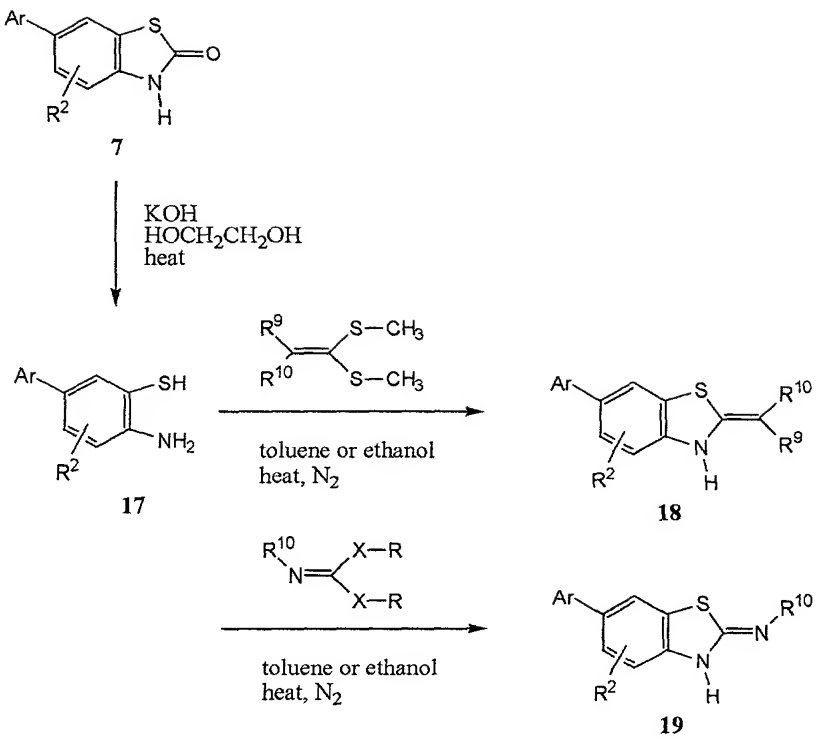
Compounds **14** and **17** can be prepared as shown in schemes V and VI from compounds **4** and **7** using strong basic conditions such as heating the compound in a mixture of potassium hydroxide and ethylene glycol at 165 °C under an inert atmosphere such as argon or nitrogen.

Scheme V


Ar
R4
N
O
N
H
R2
4
KOH
HOCH2CH2OH
NH
NH2
14
R9
S—CH3
R10
S—CH3
toluene or ethanol
heat, N2
15
X—R
X—R
16

5

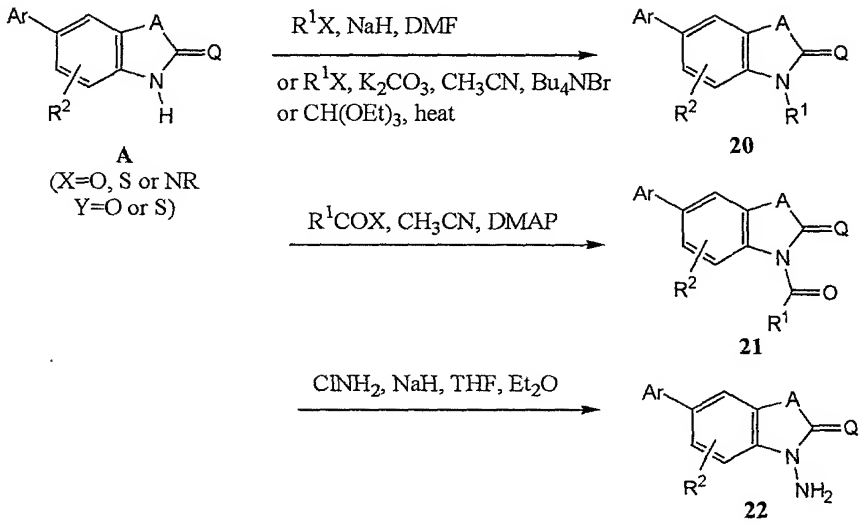
Scheme VI



As illustrated in Scheme VII, the compounds of this invention can be further derivatized at position-1 *via* numerous approaches leading to a variety of the novel compounds including **20**, **21**, and **22**. Thus, alkyl or substituted alkyl derivatives **20** can be formed by treatment of compound **A** with a suitable base such as sodium hydride in suitable solvent such as DMF under an inert atmosphere such as argon or nitrogen followed by addition of an appropriate electrophile such as an alkyl or substituted alkyl bromide, iodide, or triflate. Such transformation of **A** at position-1 can also be effected using biphasic conditions as indicated in Scheme VII in which alkylation is executed using a biphasic catalyst such as tributylammonium bromide in a suitable solvent such as acetonitrile. A further example of such modification includes

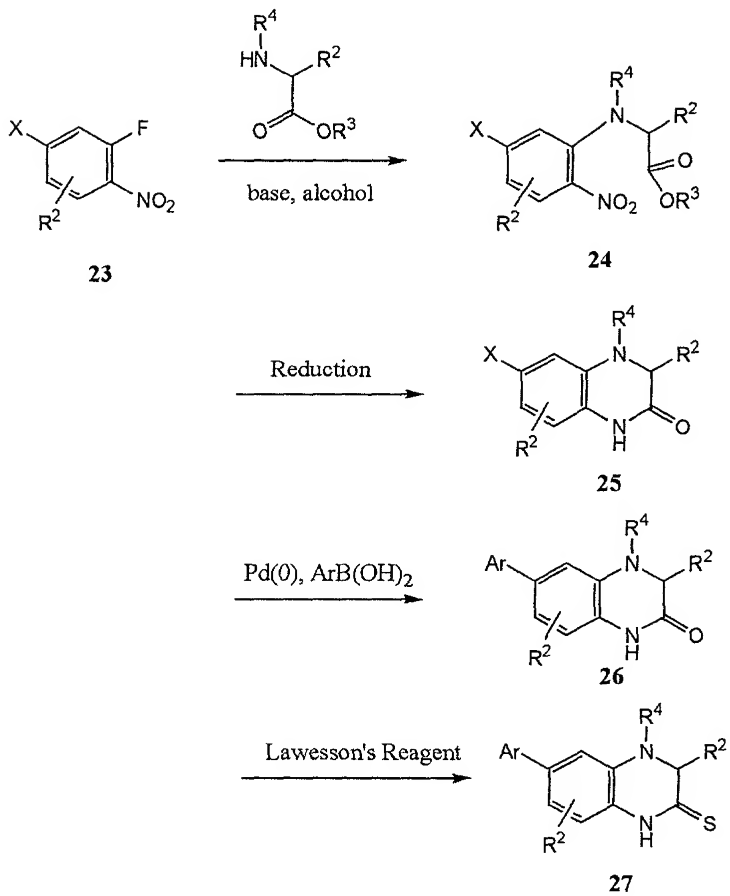
but is not limited to the one depicted in Scheme VIII via heating **A** with triethyl orthoformate to afford 1-substituted derivatives **20**.

Scheme VII



The acylation or carboxylation of the compound **A** at position-1 to give compound **21** can be readily effected by treatment of **A** with a suitable acylating or carboxylating reagent such as di-*t*-butyl dicarbonate in the presence of a suitable basic catalyst such as DMAP in a suitable solvent such as acetonitrile under an inert atmosphere such as argon or nitrogen. The amination of position-1 of compound **A** to give compound **22** can be furnished using a suitable aminating reagent such as chloroamine in the presence of a suitable base such as sodium hydride in a suitable solvent such as THF or diethyl ether following the literature procedure (Metlesics et al. *J. Org. Chem.* **30**, 1311(1965)).

Scheme VIII



Scheme VIII describes a procedure to prepare quinoxalin-4-ones. An *o*-fluoro nitro-benzene **23** (X = I, Br, Cl) is reacted with an appropriately substituted amino acid derivative in the presence of a suitable base in a protic solvent such as alcohol to give compound **24** which is readily reduced by a suitable reducing agent such as tin chloride to furnish quinoxalin-2-one **25**. The compounds of this invention, **26**, can be easily produced by coupling an appropriate aryl boronic acid with compound **25** in a similar fashion as for the preparation of compound **9**. Conversion of **26** to **27** can be readily effected following the procedure of synthesizing compound **11a**.

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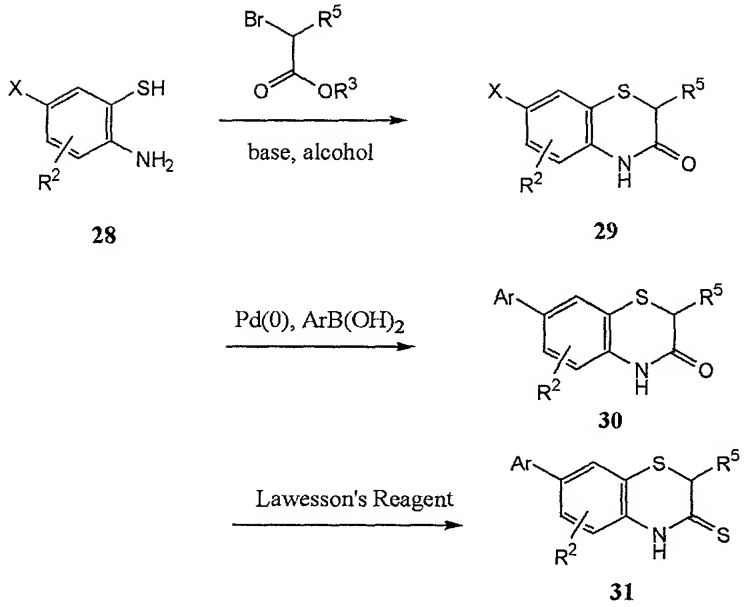
Scheme IX



Scheme IX illustrates an approach to prepare the benzothiazinones. Thus, a substituted *o*-amino benzenethiol **28** is treated with an appropriately substituted α-bromoacetate in a suitable solvent such as ethanol to afford compound **29**. Compound **29** can be readily coupled with an aryl boronic acid following the protocol of compound **9** to afford the compounds of this invention, **30**. Conversion of **30** to **31** can be carried out using a suitable sulfur reagent such as Lawesson's reagent according to procedure of synthesized compounds **11a**.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium,

potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

This invention includes pharmaceutical compositions comprising one or more compounds of this invention, preferably in combination with one or more pharmaceutically acceptable carriers and/or excipients. The invention also includes methods of contraception and methods of treating or preventing maladies associated with the progesterone receptor, the methods comprising administering to a mammal in need thereof a pharmaceutically effective amount of one or more compounds as described above wherein Q is oxygen as antagonists of the progesterone receptor. The invention further provides comparable methods and compositions which utilize one or more compounds herein wherein Q is S, NR^6, or CR^7R^8 as agonists of the progesterone receptor.

The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

When used in contraception the progesterone receptor antagonists of the current invention may be used either alone in a continuous administration of between 0.1 and 500 mg per day, or alternatively used in a different regimen which would entail 2-4 days of treatment with the progesterone receptor antagonist after 21 days of a progestin. In this regimen between 0.1 and 500 mg daily doses of the progestin (e.g. levonorgestrel, trimegestone, gestodene, norethistrone acetate, norgestimate or

cyproterone acetate) would be followed by between 0.1 and 500 mg daily doses of the progesterone receptor antagonists of the current invention.

The progesterone receptor antagonists of this invention, used alone or in combination, can also be utilized in methods of treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

The progesterone receptor agonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake.

When used in contraception the progesterone receptor agonists of the current invention are preferably used in combination or sequentially with an estrogen agonist (e.g. ethinyl estradiol). The preferred dose of the progesterone receptor agonist is between 0.01 and 500 mg per day.

This invention also includes pharmaceutical compositions comprising one or more compounds described herein, preferably in combination with one or more pharmaceutically acceptable carriers or excipients. When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or

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parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in a sustained release form. For most large mammals, the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

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These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The following non-limiting examples illustrate preparation and use of the compounds of the invention.

EXAMPLE 1

5-Bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester

Prepared *via* a literature procedure (*J. Org. Chem.* **60(6)**, 1565-82 (1995)). White solid: mp 148-149 °C; ^{1}H-NMR (DMSO-d_6) δ 11.4 (s, 1H), 7.6 (d, 1H, J = 8.57 Hz), 7.2 (dd, 1H, J = 8.57, 4.29 Hz), 7.1 (s, 1H), 1.6 (s, 9H); MS (ES) *m/z* 311([M-H]$^-$, 70%), 313 ([M-H]$^-$, 70%).

EXAMPLE 2

1-Benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one

A mixture of 5-bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester (2.5g, 8 mmol), benzyl bromide (1.2 mL, 10 mmol), potassium carbonate (1.38g, 10 mmol), and potassium iodide (50 mg) in anhydrous acetonitrile was heated at 80 °C under nitrogen for 1 hour. The reaction mixture was cooled to room temperature and treated with a saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$). After removal of the solvent, the residue was taken up in trifluoroacetic acid (10 mL, neat) and the solution was stirred at room temperature under nitrogen for 10 minutes. The reaction solution was then treated with brine (30 mL) and ethyl acetate (50 mL). The organic layer was separated and dried ($MgSO_4$). After removal of the solvent, the residue was applied to a pad of silica gel to afford the title compound as white solid (1.89, 78%): mp 245-246 °C; ^{1}H-NMR (DMSO-d_6) δ 11.2. (s, 1H), 7.37-7.27 (m, 6H), 7.13 (dd, 1H, J = 8.25, 2.25 Hz), 6.95 (d, 1H, J = 8.25 Hz), 5.0 (s, 2H); MS (ES) *m/z* 301([M - H]$^-$, 50%), 303([M - H]$^-$, 50%).

EXAMPLE 3

5-Bromo-3-methyl-2-oxo-2, 3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester

A mixture of 5-bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid tert-butyl ester (4.0 g, 12.8 mmol), iodomethane (2.74 g, 9.2 mmol), and K_2CO_3 in CH_3CN (60 mL) was stirred at room temperature under a blanket of nitrogen overnight. Upon completion of the reaction, ethyl acetate (200 mL) was added and the organic layer was washed with H_2O (200 mL), dried over Na_2SO_4, and concentrated. The residue was purified *via* chromatography (silica gel, 25% ethyl acetate/hexane) to give 5-bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-

carboxylic acid *tert*-butyl ester as a white solid: mp 98-99 °C; ^{1}H-NMR ($CDCl_3$) δ 7.7 (d, 1H, J = 8,5 Hz), 7.27 (bs, 2H), 7.09 (d, 1H, J = 2 Hz), 3.4 (s, 3H), 1.7 (s, 9H); MS (ES) *m/z* 349([M + Na]$^+$, 20%), 351([M + Na]$^+$, 20%); Anal. Calc. For $C_{13}H_{15}BrN_2O_3$: C, 47.73, H, 4.62, N, 8.56. Found: C, 47.46, H, 4.5, N, 8.29.

EXAMPLE 4

6-Bromo-1-methyl-1,3-dihydro-benzoimidazol-2-one

Prepared from 5-bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester in the same fashion as that of Example 2. White solid: mp 237-238 °C; ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.35 (d, 1H, J = 1.58 Hz), 7.14 (dd, 1H, J = 7.89, 1.58 Hz), 6.92 (d, 1H, J = 7.89 Hz), 3.3 (s, 3H); MS (ES) *m/z* 227([M + H]$^+$, 50%), 229([M + H]$^+$, 50%); Anal. Calc. For $C_8H_7BrN_2O$: C, 42.32, H, 3.11, N, 12.34 Found: C, 42.35, H, 3.07 N, 11.89.

EXAMPLE 5

1-Benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one

A mixture of 1-benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one (0.75 g, 2.5 mmol), 3-chloro-phenyl boronic acid (0.4 g, 2.6 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.23 g, 0.2 mmol), and potassium carbonate (0.72 g, 5.2 mmol) in toluene (15 mL) and H_2O (8 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then heated to 85 °C for 1 hour. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layer was washed twice with aqueous ammonium chloride (30 mL) and once with brine (30 mL), dried over magnesium sulfate and concentrated. After removal of the solvent, the residue was purified *via* chromatography (silica gel, 25% ethyl acetate/hexane) to give 1-benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one as a white solid (0.134 g, 16%): mp 168-169 °C; ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.66 (t, 1H, J = 2.05 Hz), 7.58-7.5 (m, 1H), 7.45 (t, 2H, J = 8.18 Hz), 7.37-7.22 (m, 7 H), 7.08 (d, 1H, J =

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8.18 Hz), 5.1 (s, 2H); MS (ES) *m/z* 333([M - H]$^-$, 100%); Anal. Calc. For $C_{20}H_{15}ClN_2O$: C, 71.75, H, 4.52, N, 8.37. Found: C, 70.27, H, 4.56, N, 8.0.

EXAMPLE 6

1-Benzyl-6-(3-nitro-phenyl)-1,3-dihydro-benzoimidazol-2-one

Prepared from 1-benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 202-203 °C; ^{1}H-NMR (DMSO-d_6) δ 11.2 (s, 1H), 8.38 (t, 1H, *J* = 1.97 Hz), 8.15 (dd, 1H, *J* = 7.83, 1.97 Hz), 8.80 (d, 1H, *J* = 7.83 Hz), 7.72 (t, 1H, *J* = 7.83 Hz), 7.56 (bs, 1H), 7.43-7.22 (m, 6H), 7.13 (d, 1H, *J* = 7.83 Hz), 5.1 (s, 2H); MS (ES) *m/z* 344([M - H]$^-$, 100%); Anal. Calc. For $C_{20}H_{15}N_3O_3$ 0.25 H_2O: C, 68.66, H, 4.46, N, 12.01. Found: C, 68.42, H, 4.44, N, 11.77.

EXAMPLE 7

1-Methyl-6-(3-nitro-phenyl)-1, 3-dihydro-benzoimidazol-2-one

Prepared from 1-methyl-6-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 264-265 °C; ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 8.47 (t, 1H, *J* = 1.5 Hz), 8.19-8.15 (m, 2H), 7.75 (t, 1H, *J* = 8.25 Hz), 7.58 (d, 1H, *J* = 1.5 Hz), 7.43 (dd, 1H, *J* = 8.25, 1.5 Hz), 7.1 (d, 1H, *J* = 8.25 Hz), 3.37 (s, 3H); MS (ES) *m/z* 268([M - H]$^-$, 50%); Anal. Calc. For $C_{14}H_{11}N_3O_3$: C, 62.45, H, 4.12, N, 15.61. Found: C, 61.48, H, 4.36 N, 14.75.

EXAMPLE 8

6-(3-chloro-phenyl)-1-methyl-1,3-dihydro-benzoimidazol-2-one

Prepared from 1-methyl-6-bromo-1, 3-dihydro-benzoimidazol-2-one and 3-chloro-phenyl boronic acid in the same fashion as that of Example 5. mp 219-220 °C; ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.75 (bs, 1H), 7.65 (dd, 1H, *J* = 7.5, 1.76 Hz), 7.49-7.44 (m, 2H), 7.39-7.32 (m, 2H), 7.06 (d, 1H, *J* = 7.94 Hz), 3.35 (s, 3H); MS

10027459.062402

(ES) m/z 259([M + H]$^+$, 100%); Anal. Calc. For $C_{14}H_{11}ClN_2O$: C, 65, H, 4.29, N, 10.83. Found: C, 64.44, H, 4.36 N, 10.6.

EXAMPLE 9

5-(3-Nitro-phenyl)-1,3-dihydro-benzoimidazol-2-one

Prepared from 5-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 324-325 °C; ^{1}H-NMR (DMSO-d_6) δ 10.8 (s, 2H), 8.4 (m, 1H), 8.15 (d, 1H, J = 7.5 Hz), 8.1 (d, 1H, J = 7.5 Hz), 7.7 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 7.3 (s, 1H), 7.05 (d, 1H, J = 7.5 Hz); MS (ES) m/z 254 ([M - H]$^-$, 100%); Anal. Calc. For $C_{13}H_9N_3O_3$: C, 61.18, H, 3.55, N, 16.46. Found: C, 60.5, H, 3.69 N, 15.53.

EXAMPLE 10

4-Amino-3'-nitro-biphenyl-3-ol

4-Amino-3-methoxy-3'-nitro-biphenyl was prepared from 4-bromo-2-methoxyaniline (*Synth. Commun.* **23(6)**, 855-9(1993).) and 3-nitrophenyl boronic acid according to the procedure of Example 5. White solid: mp 167-168 °C; ^{1}H-NMR ($CDCl_3$) δ 8.39 (t, 1H, J = 1.97 Hz), 8.13-8.09 (m, 1H), 7.88-7.84 (m, 1H), 7.55 (t, 1H, J = 8.0 Hz), 7.09 (dd, 1H, J = 7.98, 1.94 Hz), 7.04 (d, 1H, J = 1.89 Hz), 6.80 (d, 1H, J = 8.04 Hz), 4.0 (s, 5H).

4-Amino-3-methoxy-3'-nitro-biphenyl was then stirred with boron tribromide in dichloromethane to give 4-amino-3'-nitro-biphenyl-3-ol as an orange solid: mp 175-176 °C; ^{1}H-NMR (DMSO-d_6) δ 9.3 (s, 1H), 8.25 (bs, 1H), 8.05 (d, 1H, J = 8.33 Hz), 7.95 (d, 1H, J = 8.33 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.06-7.02 (m, 2H), 6.70 (d, 1H, J = 8.33 Hz), 4.9 (s, 2H); MS (ES) m/z 229 ([M - H]$^-$, 100%).

10074683 .021202

EXAMPLE 11

6-(3-Nitro-phenyl)-3H-benzooxazol-2-one

A solution of 4-amino-3'-nitro-biphenyl-3-ol (0.115 g, 0.5 mmol) in dry THF (2.5 mL) was treated with a solution of 1,1'-carbonyldiimidazole (0.098 g, 0.6 mmol) in dry THF (2.5 mL). The reaction mixture was stirred at room temperature under a blanket of nitrogen for 6 hours. A precipitate formed, was collected and washed with methylene chloride (50 mL) to give 6-(3-nitro-phenyl)-3H-benzooxazol-2-one (0.095 g, 74%) as a white solid: mp 280-281 °C; ^{1}H-NMR (DMSO-d_6) δ 11.7 (s, 1H), 8.43 (t, 1H, J = 1.15 Hz), 8.2-8.13 (m, 2H), 7.79-7.72 (m, 2H), 7.59 (dd, 1H, J = 8.08, 2.31 Hz), 7.21 (d, 1H, J = 8.08 Hz), MS (ES) *m/z* 255([M - H]$^-$, 100%); Anal. Calc. For $C_{13}H_8N_2O_4$: C, 60.94, H, 3.15, N, 10.93. Found: C, 59.95, H, 3.17 N, 10.77.

EXAMPLE 12

6-(3-Nitro-phenyl)-3H-benzothiazol-2-one

A mixture of 6-bromo-2-benzothiazolinone (5.0 g, 21.7 mmol), 3-nitrophenyl boronic acid (5.0 g, 30.0 mmol), tetrakis(triphenylphosphine)-palladium (0) (1.73 g, 1.5 mmol), and potassium carbonate (8.0 g, 58.0 mmol) in toluene (100 mL), H_2O (20 mL), and ethanol (30 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 85 °C for 24 hours. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layer was washed with aqueous ammonium chloride (2x50 mL) and with brine (100 mL), dried over magnesium sulfate and concentrated. The residue was purified via chromatography (silica gel, 25% ethyl acetate/hexane) to give 6-(3-nitro-phenyl)-3H-benzothiazol-2-one as a brown solid (0.1 g, 1.8 %): mp 276-277 °C; ^{1}H-NMR (DMSO-d_6) δ 11 (s, 1H), 8.44 (t, 1H, J = 2.7 Hz), 8.21-8.08 (m, 3H), 7.78-7.69 (m, 2H), 7.24 (d, 1H, J = 9.23 Hz); MS (ES) *m/z* 271 ([M - H]$^-$, 100%); Anal. Calc. For $C_{13}H_8N_2O_3S$ 0.25 H_2O: C, 56.41, H, 3.10, N, 10.12. Found: C, 56.48, H, 3.11, N, 9.99.

EXAMPLE 13

6-(3-Chloro-phenyl)-3H-benzothiazol-2-one

Prepared from 6-bromo-2-benzothiazolinone, 3-chlorophenyl boronic acid according to the procedure of example 12. A white solid: mp 195-196 °C; ^{1}H-NMR (DMSO-d_6) δ 11.95 (s, 1H), 7.96 (d, 1H, J = 1.17 Hz), 7.7 (t, 1H, J = 1.76 Hz), 7.62-7.59 (m, 2H), 7.46 (t, 1H, J = 7.65 Hz), 7.4-7.38 (m, 1H), 7.18 (d, 1H, J = 8.24 Hz); MS (EI) *m/z* 261 (M^+, 30%); Anal. Calc. For $C_{13}H_8ClNOS \cdot 0.5\ H_2O$: C, 57.67, H, 3.35, N, 5.17. Found: C, 57.98, H, 3.11, N, 4.98.

EXAMPLE 14

7-(3-Nitro-phenyl)-4H-benzo[1,4]thiazin-3-one

A mixture of 2-amino-5-bromo-benzenethiol (20 g, 0.1 mol), ethyl bromoacetate (19 g, 0.1 mol), and sodium bicarbonate (8.8 g, 0.1 mol) in DMF (200 ml) was heated to reflux for 2 hours. The mixture was diluted with water and extracted with ethyl acetate (2x100 mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated to obtain the crude 7-bromo-4H-benzo[1,4]thiazin-3-one (20 g, 82%). A small portion of sample was recrystallized from ethanol to afford pure 7-bromo-4H-benzo[1,4]thiazin-3-one: mp 212 –213 °C; MS (EI) *m/z* 243/245 (M^+).

A solution of 7-bromo-4H-benzo[1,4]thiazin-3-one (2 g, 8.2 mmol), 3-nitrophenyl boronic acid (2.72 g, 16.4 mmol), potassium carbonate (6.85 g, 49.2 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.95 g, 0.82 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated to obtain crude 7-(3-nitro-phenyl)-4H-benzo[1,4]thiazin-3-one (0.15 g, 6%). Recrystallization of crude sample from EtOAc afforded the title compound: mp 290–292 °C; MS (EI) *m/z* 286 (M^+).

EXAMPLE 15

2-Ethyl-7-(3-nitro-phenyl)-4H-benzo[1,4]thiazin-3-one

To a mixture of 2-amino-5-bromo-benzenethiol (20 g, 0.1 mol) and cesium carbonate (33 g, 0.1 mol) in DMF (500 ml) at –35 °C was added dropwise 2-bromobutyrylbromide (23 g, 0.1 mol). The mixture was allowed to warm to room temperature, poured into ice/water, and extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, ethyl acetate:hexane/1:6) to afford 7-bromo-2-ethyl-4H-benzo[1,4]thiazin-3-one (3.7 g, 14%): mp 100 °C; MS (EI) *m/z* 271/273 (M^+).

A solution of 7-bromo-2-ethyl-4H-benzo[1,4]thiazin-3-one (2 g, 7.3 mmol), 3-nitrophenyl boronic acid (1.22 g, 7.3 mmol), potassium carbonate (3 g, 22 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.84 g, 0.72 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x40 mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was recrystallized from ethanol to afford the title compound as tan crystals (0.17 g, 7.3%): mp 180 °C; MS (EI) *m/z* 314 (M^+).

EXAMPLE 16

8-(3-Chloro-phenyl-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one

To a mixture of acetic acid (500 ml), 30% hydrogen peroxide (250 ml), and concentrated sulfuric acid (10 ml) was added 4-bromo-2-fluoroaniline (50 g, 0.26 mol) at 85 ± 5 °C over 20 minutes. The reaction mixture was allowed to cool to room temperature and filtered. The solution was diluted with water and extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water, then

brine, dried ($MgSO_4$) and evaporated. The semisolid residue was filtered and the crude 4-bromo-2-fluoro-1-nitro-benzene was sublimed *in vacuo* to afford 4-bromo-2-fluoro-1-nitro-benzene (23 g, 40%): mp 82–83 °C; ^{1}H-NMR (DMSO-d_6) δ 7.64 – 7.70 (m, 1H), 8.0 (dd, 1H, J = 11.0, 1.98 Hz), 8.1 (t, 1H, J = 8.57 Hz); MS (EI) *m/z* 219/221 (M^+).

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (9 g, 40 mmol), L-proline (4.6g, 40 mmol), and potassium carbonate (7 g, 50 mmol) in ethanol (50 ml) and water (40 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water and was adjusted to pH 6 with 1N aqueous HCl solution. The mixture was extracted with EtOAc (2x100 mL), the combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated to afford *N*-(5-bromo-2-nitro-phenyl)-pyrrolidine-2-carboxylic acid (6 g, 48%) which was used in the next step without further purification.

A solution of *N*-(5-bromo-2-nitro-phenyl)-pyrrolidine-2-carboxylic acid (6g, 23 mmol) and tin(II) chloride dihydrate (16.5 g, 73 mmol) in ethanol (200 ml), water (30 ml) and concentrated HCl (10 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and was adjusted to pH 9 with 2N aqueous sodium hydroxide solution. After addition of EtOAc, the precipitated tin hydroxide was filtered off. The layers were separated and the organic layer was washed with water, then brine, dried ($MgSO_4$) and evaporated to afford 8-bromo-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one (3.7 g, 60%), which was used without further purification.

A solution of 8-bromo-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one (2.7 g, 10 mmol), 3-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.5 g, 0.43 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x60 mL). The combined organic extracts were washed with

water, then brine, dried ($MgSO_4$) and evaporated. The crude product (1.5 g) was recrystallized from EtOAc/hexane to afford the title compound (0.2 g, 7%): mp 210 °C; MS (+APCI) *m/z* 299 ($[M+H]^+$).

EXAMPLE 17

6-(3-Chloro-phenyl)-4-methyl-3,4-dihydro-1H-quinoxalin-4-one

(5-Bromo-2-nitro-phenyl)-methyl-amino]-acetic acid.

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (9 g, 40 mmol), sarcosine (3.6g, 40 mmol), and potassium carbonate (5.5 g, 40 mmol) in ethanol (100 ml) and water (40 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water and was adjusted to pH 6 with 1N aqueous HCl solution. The yellow precipitate was collected, washed with water and dried *in vacuo* to obtain crude [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid (10 g, 87%). A portion of the crude sample was recrystallized from EtOAc/hexane to afford the pure [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid: mp 152–155 °C; ^{1}H-NMR (DMSO-d_6) δ 2.81 (s, 3H), 4.00 (s, 2H), 7.06 (dd, 1H, J = 8.79, 1.98 Hz), 7.22 (d, 1H, J = 1.98 Hz), 7.69 (d, 1H, J = 8.79 Hz), 12.8 (s, 1H); MS (+APCI) *m/z* 289/291 $(M+H)^+$.

A solution of [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid (8g, 27.6 mmol) and tin(II) chloride dihydrate (20 g, 88 mmol) in ethanol (200 ml), water (30 ml) and concentrated HCl (10 ml) was heated to reflux for 6 hours. After cooling to room temperature the mixture was diluted with water and was adjusted to pH 9 with 2N aqueous sodium hydroxide solution. After addition of EtOAc, the precipitated tin hydroxide was filtered off. The layers were separated and the organic layer was washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was recrystallized from ethanol to afford 6-bromo-4-methyl-3,4-dihydro-1H-quioxalin-2-one (2.4 g, 36%), which was used without further purification. ^{1}H-NMR (DMSO-d_6)

δ 2.78 (s, 3H), 3.89 (s, 2H), 6.81 (d, 1H, J = 1.76 Hz), 6.95 (dd, 1H, J = 8.49, 1.81 Hz), 7.05 (d, 1H, J = 8.47 Hz), 10.63 (s, 1H).

A solution of 6-bromo-4-methyl-3,4-dihydro-1H-quioxalin-2-one (2.4 g, 10 mmol), 3-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.5 g, 0.43 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, EtOAc:hexane/1:6) to afford the title compound (0.58 g, 21%): mp 140 °C; ^{1}H-NMR (DMSO-d_6) δ 2.82 (s, 3H), 3.65 (s, 2H), 6.82 (d, 1H, J = 7.91 Hz), 6.90 (d, 1H, J = 1.76 Hz), 6.99 (dd, 1H, J = 8.13, 1.98 Hz), 7.3–7.32 (m, 1H), 7.39 (t, 1H, J = 7.91 Hz), 7.55 (dt, 1H, J = 7.91, 1.10 Hz), 7.64 (t, 1H, J = 1.98 Hz), 10.47 (s, 1H); MS ((+)APCI) m/z 299 $(M+H)^+$.

EXAMPLE 18

5-(3, 4-Dihydro-4-methyl-2-oxo-quinaxalin-6-yl) thiophene-3-carbonitrile

3,4-Dihydro-4-methyl-2-oxo-quinoxalin-6-yl) boronic acid.

To a solution of 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (3.6g, 15 mmol) in THF (100ml) was added sodium hydride (0.6g, 15 mmol, 60% dispersion in mineral oil). After stirring 30 min. at room temperature, the mixture was cooled to -78°C and butyl lithium (2.5M in hexanes, 6 ml, 15 mmol) was added slowly. After 30 min. triisopropyl borate (7ml, 30 mmol) was added and the mixture was allowed to warm to room temperature. After 2 hrs. hydrochloric acid (1N, 200 ml) and EtOAc (200 ml) were added. After stirring for 30 min., the pH was adjusted to 6 and the layers were separated. The aqueous phase was extracted with EtOAc, then the combined organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, the precipitate was filtered off and

dried in vacuo to obtain the subtitled compound (1.6g, 52%) as an off-white solid: ^{1}H-NMR (DMSO-d_6) δ 2.78 (s, 3H), 3.62 (s, 2H), 6.75 (d, J = 7.58Hz, 1H), 7.16 (s,1H), 7.18 (d, J = 7.86 Hz, 1H), 7.85 (s, 2H), 10.45 (s, 1H). MS (EI) m/z 207 $(M+H)^+$.

A mixture of 3,4-dihydro-4-methyl-2-oxo-quinoxalin-6-yl) boronic acid (1.6g, 80 mmol), 2-bromo-4-cyanothiophene (1.5 g, 80 mmol), potassium carbonate (3.3g, 24 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.25g, 0.2 mmol) in dimethoxyethane (70 ml), ethanol (15 ml), and water (15 ml) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc (3x40 mL). The combined organic layers were washed with water, then brine, dried ($MgSO_4$) and evaporated to obtain crude product (0.85g, 40%). The residue was purified by column chromatography (SiO_2, 40% acetonitrile, 60% water) to afford the title compound: mp 270 °C; ^{1}H-NMR (DMSO-d_6) δ 2.84 (s, 3H), 3.70 (s, 2H), 6.82 (d, J = 7.91 Hz, 1H), 6.96 (d, J = 1.76 Hz, 1H), 7.02 (dd, J = 7.91, 1.76 Hz, 1H), 7.83 (d, J = 1.32 Hz, 1H) 8.44 (d, J = 1.32 Hz, 1H), 10.56 (s, 1H); MS (EI) m/z 269 (M^+).

EXAMPLE 19

4-(*n*-Butyl)-6-(3-chloro-phenyl)-3,4-dihydro-1H quinoxalin-2-one

[(5-Bromo-2-nitro-phenyl)-*n*-butyl-amino]acetic acid

A mixture of 4-bromo-2-fluoro-nitro benzene (34 g, 0.15 mol), N-*n*-butyl glycine (20 g, 0.15 mol) in ethanol (600 ml), and water (150 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with 2N sodium hydroxide, extracted with CH_2Cl_2 and the pH was adjusted to 5 with 1N HCl. The mixture was extracted with CH_2Cl_2, the CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated to obtain the crude product (11 g, 22%) as a brown oil, which was used without further purification. ^{1}H-NMR (DMSO-d_6) δ 0.84 (t, J = 7.30 Hz, 3H), 1.23 (m, 2H), 1.45 (m, 2H), 3.18 (t, J = 7.30 Hz, 2H), 3.91 (s, 2H), 7.16 (dd, J = 8.68, 1.91 Hz, 1H), 7.40 (d, J = 1.94 Hz, 1H), 7.69 (d, J = 8.68 Hz, 1H); MS (EI) m/z 331 (M^+).

<u>6-Bromo-4-(n-butyl)-3,4-dihydro-1H-quinoxalin-2-one.</u>

To a solution of [(5-bromo-2-nitro-phenyl)-n-butyl-amino]acetic acid (11g, 33 mmol) in acetic acid (150 ml) was added iron powder (6g, 107 mmol) and the mixture was stirred for 2 hrs at 90°C. The reaction mixture was cooled and filtered and the acetic acid was evaporated. The remaining slurry was extracted with CH_2Cl_2 (3x50 mL). The combined CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and evaporated (8.5 g, 90%). The product was used without further purification. ^{1}H-NMR (DMSO-d_6) δ 0.93 (t, J = 6.81 Hz, 3H), 1.35 (m, 2H), 1.51 (m, 2H), 3.18 (t, J = 6.92 Hz, 2H), 3.75 (s, 2H), 6.6-6.9 (m, 3H), 10.50 (s, 1H).

A solution of 6-bromo-4-(n-butyl)-3,4-dihydro-1H-quinoxalin-2-one (8.5g, 30 mmol), 3-chlorophenyl boronic acid (5g, 30 mmol), potassium carbonate (12.5g, 90 mmol) and tetrakis- (triphenylphosphine) palladium (0) (1.3g, 1.1 mmol) in dimethoxyethane (200 ml), ethanol (50 ml), and water (50 ml) was heated to reflux for 6 hrs. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with water, then brine, dried ($MgSO_4$) and evaporated to obtain crude product (7g, 74%). The residue was purified by column chromatography (SiO_2, 20% EtOAc, 80% hexane) to afford the title compound, mp 110-115°C. ^{1}H-NMR (DMSO-d_6) δ 0.93 (t, J = 7.35 Hz, 3H), 1.36 (m, 2H), 1.56 (m, 2H), 3.30 (m, 2H), 3.74 (s, 2H), 6.84 (d, J = 8.13 Hz, 1H), 6.90 (d, J = 1.54 Hz, 1H), 6.95 (dd, J = 8.13, 1.54 Hz, 1H) 7.35 (m, 1H), 7.43 (t, J = 7.91 Hz, 1H), 7.55 (m, 1H), 7.63 (t, J = 1.76 Hz, 1H), 10.50 (s, 1Hz). MS ([+] APC I) m/z 315 $[M+H]^+$ + 1 chlorine.

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EXAMPLE 20

6-(3-Cyano-5-fluorophenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one

[(5-Bromo-2-nitro-phenyl)-isopropyl-amino]-acetic acid. A mixture of 4-bromo-2-fluoro-1-nitrobenzene (52 g, 0.24 mol), n-isopropylglycine (26 g, 0.22 mol), potassium carbonate (32 g, 0.23 mol) in ethanol (700 ml) and water (140 ml) was heated to reflux for 3 hrs. After cooling to room temperature the mixture was diluted with water, extracted with $CHCl_3$, and the pH was adjusted to 5 with 1N HCl. The yellow precipitate was filtered off, washed with water and dried in vacuo (31 g, 44%): ^{1}H-NMR (DMSO-d_6) δ 1.08 (d, J = 6.50 Hz, 6H), 3.55 (septet, J = 6.50 Hz, 1H), 3.92 (s, 2H), 7.25 (dd, J = 8.65, 1.72 Hz, 1H), 7.53 (d, J = 1.69 Hz, 1H), 7.69 (d, J = 8.65 Hz, 1H), 12.52 (bs, 1H).

6-Bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one. To a solution of [(5-bromo-2-nitro-phenyl)-isopropyl-amino] acetic acid (27 g, 85 mmol) in acetic acid (400 ml) was added iron powder (15 g, 0.27 mol) and the mixture was stirred for 2 hrs. at 90 °C. The reaction mixture was cooled, filtered, and the acetic acid was evaporated. The remaining slurry was extracted with CH_2Cl_2 (3 x 300 ml). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$) and evaporated to afford the subtitled compound (16.8 g, 73%): ^{1}H-NMR (DMSO-d_6) δ 1.13 (d, J = 6.54 Hz, 6H), 3.57 (s, 2H), 3.99 (septet, J = 6.54 Hz, 1H), 6.82 (dd, J = 8.23, 1.88 Hz, 1H), 6.72 (d, J = 8.17 Hz, 1H), 6.90 (d, J = 1.59 Hz, 1H), 10.50 (s, 1H): MS (EI) 267/269 $(M)^+$ + 1 bromine.

(4-Isopropyl-2-oxo-3,4-dihydro-quinoxalin-6-yl)boronic acid.

To a solution of 6-bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one (8.1 g, 30 mmol) in THF (200 ml) was added sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol). After stirring for 30 min. at room temperature, the mixture was cooled to -78 °C and butyl lithium (2.5 M in hexanes, 12.5 ml, 30 mmol) was added slowly. After 30 min. triisopropyl borate (19 ml, 83 mmol) was added and the mixture was allowed to warm to room temperature. After 2 hrs. hydrochloric acid (1N, 350

ml) and ethyl acetate (350 ml) were added. After stirring for 30 min., the pH was adjusted to 6 and the layers were separated. The aqueous phase was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, the precipitate filtered off and dried in vacuo to obtain the subtitled compound (3.5 g, 50%) as an off-white solid that was used without further purification. ^{1}H-NMR (DMSO-d_6) δ 1.15 (d, J = 6.56 Hz, 6H), 3.51 (s, 2H), 4.04 (septet, J = 6.57 Hz, 1H), 6.76 (d, J = 7.65 Hz, 1H), 7.14 (d, J = 7.66 Hz, 1H), 7.27 (s, 1H), 7.84 (s, 2H), 10.41 (s, 1H).

A solution of (3,4-dihydro-4-isopropyl-2-oxoquinoxalin-6-yl)boronic acid (1.15 g, 4.9 mmol), 3-bromo-5-fluoro-benzonitrile (1.08 g, 5.4 mmol), potassium carbonate (2.75 g, 22 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.25 g, 0.2 mmol) in dimethoxyethane (70 ml), ethanol (15 ml) and water (15 mol) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was concentrated and the residue was dissolved in ethyl acetate and 2N sodium hydroxide. The organic layer was washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, and the precipitate was filtered off to afford the title compound, mp 238-240 °C (0.5 g, 30%); ^{1}H-NMR (DMSO-d_6) δ 1.17 (d, J = 6.49 Hz, 6H), 3.59 (s, 1H), 4.30 (septet, J = 6.54 Hz, 1H), 6.89 (d, J = 8.00 Hz, 1H), 7.11 (d, J = 8.08 Hz, 1H), 7.76 (d, J = 8.34 Hz, 1H), 7.91 (d, J = 10.47 Hz, 1H), 8.06 (s, 1H), 10.56 (s, 1H). MS (ESI) m/z 308 $[M-H]^-$.

EXAMPLE 21

6-(3-Chloro-4-fluoro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of (3,4-dihydro-4-isopropyl-2-oxoquinoxalin-6-yl)boronic acid (2.4 g, 10 mmol), 4-bromo-2-chlorofluorobenzene (2 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.46 g, 0.4 mmol) in dimethoxyethane (100 ml), ethanol (25 ml) and water (25 mol) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were washed with

water, then brine, dried ($MgSO_4$) and evaporated to obtain crude product (2.9 g, 91%). Recrystallization from EtOAc/hexane afforded the title compound, mp 208-213 °C: ^{1}H-NMR (DMSO-d_6) δ 1.16 (d, J = 6.59 Hz, 6H), 3.56 (s, 2H), 4.22 (septet, J = 6.59 Hz, 1H), 6.86 (d, J = 7.91 Hz, 1H), 6.96 (dd, J = 7.91, 1.76 Hz, 1H), 7.01 (d, J =1.76 Hz, 1H), 7.43 (t, J = 9.01 Hz, 1H), 7.61 (m, 1H), 7.82 (dd, J = 7.14, 2.31 Hz, 1H), 10.47 (s, 1H). MS (EI) m/z 318 $[M]^+$ + 1 chlorine.

EXAMPLE 22

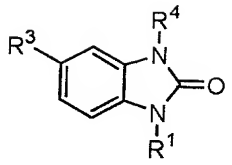
6-(3-Chloro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of 6-bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one (2 g, 75 mmol), 3-chlorophenylboronic acid (1.6 g, 10 mmol), potassium carbonate (4g, 30 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.4 g, 0.35 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic layers were washed with water, then brine, dried ($MgSO_4$) and evaporated to give crude product (1.5 g, 66%). Recrystallization from EtOAc/hexane afforded the title compound: mp 146-150 °C. ^{1}H-NMR (DMSO-d_6) δ 1.16 (d, J = 6.37 Hz, 6H), 3.57 (s, 2H), 4.21 (septet, J= 6.59 Hz, 1H), 6.87 (d, J = 7.91 Hz, 1H), 6.98 (dd, J = 7.91, 1.76 Hz, 1H), 7.02 (d, J = 1.76 Hz, 1H), 7.35 (m, 1H), 7.43 (t, J = 7.69 Hz, 1H), 7.57 (m, 1H), 7.66 (t, J = 1.76 Hz, 1H), 10.48 (s, 1H). MS (EI) m/z 300 $(M)^+$ + 1 chlorine.

EXAMPLE 23 -Pharmacology

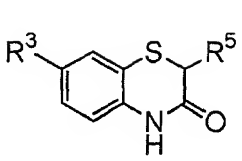
The compounds of this invention were tested in the relevant assay as described below and their potency are in the range of 0.01 nM to 5 mM in the *in vitro* assays and 0.001 to 300 mg/kg in the *in vivo* assays. The selected examples are listed in Table 1 and 2.

Table 1

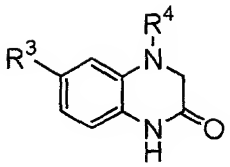


Compound	R^3	R^4	R^1	Alkaline Phosphatase IC_{50} (nM)	hPR CV-1 IC_{50} (nM)
1	3-chlorophenyl	Bn	H		412
2	3-nitrophenyl	Bn	H		230
3	3-chlorophenyl	Me	H		1370
4	3-nitrophenyl	Me	H		1529
5	3-nitrophenyl	H	Me		750
6	3-nitrophenyl	isopropyl	H		147
7	3-chlorophenyl	isopropyl	H		155

Table 2



B



C

Compound	R^3	R^4	Alkaline Phosphatase IC_{50} (nM)	hPR CV-1 IC_{50} (nM)
B1	3-nitrophenyl	H		220
B2	3-nitrophenyl	Et		295
C1	3-chlorophenyl	Me	600	1585
C2	3-chlorophenyl	H	550	525
C3	2-(4-cyanothio-phenyl)	Me	300	
C4	3-chlorophenyl	isopropyl	850	
C5	3-chloro-4-fluoro-phenyl	isopropyl	700	
C6	3-chlorophenyl	*n*-Bu	500	

1. T47D cell proliferation assay

The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The materials and methods used in this assay are as follows.

a. Growth medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Treatment medium: Minimum Essential Medium (MEM) (#51200-038GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment. Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progestin and antiprogestin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progestin agonist. Twenty-four hours after treatment, the medium is discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 µl of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

e. Analysis of Results:

Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 3. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for individual studies

		EC_{50}		95% CI	
Compound	Exp	(nM)	SE	lower	upper
Trimegestone	1	0.017	0.003	0.007	0.040
	2	0.014	0.001	0.011	0.017
	3	0.019	0.001	0.016	0.024
MPA	1	0.019	0.001	0.013	0.027
	2	0.017	0.001	0.011	0.024

Table 4. Estimated IC_{50}, standard error, and 95% confident interval for the antiprogestin, RU486

		IC_{50}		95% CI	
Compound	Exp	(nM)	SE	lower	upper
RU486	1	0.011	0.001	0.008	0.014
	2	0.016	0.001	0.014	0.020
	3	0.018	0.001	0.014	0.022

EC_{50}: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC_{50}: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

2. Rat decidualization assay

The objective of this procedure is used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and compare the relative potencies of various test compounds. The materials and methods used in this assay are as follows.

a. Methods: Test compounds are dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (Mazola™) are then prepared by heating (~80 °C) the mixture to evaporate ethanol. Test compounds are subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

b. Animals (RACUC protocol #5002)

Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) are obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy is performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals are housed under 12 hr light/dark cycle and given standard rat chow and water *ad libitum.*

c. Treatment

Rats are weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 ml vehicle are administered by subcutaneous injection in the nape of the neck or by gavage using 0.5 ml. The animals are treated once daily for seven days. For testing antiprogestins, animals are given the test compounds and a EC_{50} dose of progesterone (5.6 mg/kg) during the first three days of treatment. Following decidual stimulation, animals continue to receive progesterone until necropsy four days later.

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d. Dosing

Doses are prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle is included. Determination of dose-response curves is carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg).

e. Decidual induction

Approximately 24 hr after the third injection, decidualization is induced in one of the uterine horns by scratching the antimesometrial luminal epithelium with a blunt 21 G needle. The contralateral horn is not scratched and serves as an unstimulated control. Approximately 24 hr following the final treatment, rats are sacrificed by CO_2 asphyxiation and body weight measured. Uteri are removed and trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns are weighed separately.

f. Analysis of Results:

The increase in weight of the decidualized uterine horn is calculated by D-horn/C-horn and logarithmic transformation is used to maximize normality and homogeneity of variance. The Huber M-estimator is used to down weight the outlying transformed observations for both dose-response curve fitting and one-way analysis of variance. JMP software (SAS Institute, Inc.) is used for both one-way ANOVA and non-linear dose-response analyses.

g. Reference Compounds:

All progestin reference compounds were run in full dose-response curves and the EC_{50} for uterine wet weight were calculated.

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Table 5. Estimated EC_{50}, standard error (SE), and 95% confidence intervals for individual studies

Compound	Exp	EC_{50} (mg/kg, s.c.)	SE	95% CI lower	95% CI upper
Progesterone	1	5.50	0.77	4.21	7.20
	2	6.21	1.12	4.41	8.76
3-Ketodesogestrel	1	0.11	0.02	0.07	0.16
	2	0.10	0.05	0.11	0.25
	3	0.06	0.03	0.03	0.14
Levonorgestrel	1	0.08	0.03	0.04	0.16
	2	0.12	0.02	0.09	0.17
	3	0.09	0.02	0.06	0.13
	4	0.09	0.02	0.06	0.14
MPA	1	0.42	0.03	0.29	0.60
	2	0.39	0.05	0.22	0.67
	3	0.39	0.04	0.25	0.61

Table 6. Estimated average EC_{50}, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds

Compound	EC50 (mg/kg, s.c.)	SE	95% CI lower	95% CI upper
Progesterone	5.62	0.62	4.55	7.00
3-Ketodesogestrel	0.10	0.02	0.07	0.14
Levonorgestrel	0.10	0.01	0.08	0.12

Table 7. Estimated IC_{50}, standard error, and 95% confident interval for the antiprogestin, RU 486

Compound	Exp.	IC_{50} (mg/kg, p.o.)	SE	95% CI lower	95% CI upper
RU 486	1	0.21	0.07	0.05	0.96
	2	0.14	0.02	0.08	0.27

Concentration: Compound concentration in assay(default-mg/kg body weight)

Route of administration: Route the compound is administered to the animals

Body weight: Mean total animal body weight (default-kg)

D-horn: Wet weight of decidualized uterine horn (default-mg)

C-horn: Wet weight of control uterine horn (default-mg)

Decidual response: [(D-C)/C]x100%

Progestational activity: Compounds that induce decidualization significantly ($p<0.05$) compared to vehicle control are considered active

Antiprogestational activity: Compounds that decrease EC_{50} progesterone induced decidualization significantly ($p<0.05$)

EC_{50} for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

IC_{50} for uterine weight: Concentration of compound that gives half-maximal decrease in EC_{50} progesterone induced decidual response (default-mg/kg)

3. PRE-luciferase assay in CV-1 cells

The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Growth medium: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM

GlutaMax (GIBCO, BRL). Experimental medium: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using 1.2×10^7 cells, 5 mg pLEM plasmid with hPR-B inserted at Sph1 and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 µl. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty µl of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

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d. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 8. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

		EC50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

Table 9. Estimated IC_{50}, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies

		IC 50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
RU486	1	0.028	0.002	0.019	0.042
	2	0.037	0.002	0.029	0.048
	3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p<0.05$) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p<0.05$)

EC_{50}: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC_{50}: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

4. T47D cell alkaline phosphatase assay

The purpose of this assay is to identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells. The materials and methods used in this assay are as follows.

a. Culture medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 µg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Alkaline phosphatase assay buffer:

I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100

II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

c. Cell Culture and Treatment:

Frozen T47D cells were thawed in a 37°C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 µl of diluted cell suspension was added. Twenty µl of reference or test compounds diluted in the culture medium was then added to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO_2/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

At the end of treatment, the medium was removed from the plate and fifty µl of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 µl of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

e. Analysis of Results: Analysis of dose-response data

For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the EC_{50} or IC_{50} values are calculated.

Table 10. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments

Compound	Exp.	EC50 (nM)	SE	95% CI lower	95% CI upper
Progesterone	1	0.839	0.030	0.706	0.996
	2	0.639	0.006	0.611	0.669
	3	1.286	0.029	1.158	1.429
Trimegestone	1	0.084	0.002	0.076	0.091
	2	0.076	0.001	0.072	0.080
	3	0.160	0.004	0.141	0.181

Table 11. Estimated IC_{50}, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments

Compound	Exp	IC 50 (nM)	SE	95% CI lower	95% CI upper
RU486	1	0.103	0.002	0.092	0.115
	2	0.120	0.001	0.115	0.126
	3	0.094	0.007	0.066	0.134

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EXAMPLE 24

1-Benzyl-6-(3-chlorophenyl)-1,3-dihydro-2H-benzimidazole-2-thione

To a solution of 1-benzyl-6-(3-chlorophenyl)-1,3-dihydro-2H-benzimidazole-2-one (0.1g, 0.3 mmol) in anhydrous toluene was added under a blanket of nitrogen Lawesson's reagent (0.133g, 0.33 mmol). The mixture was heated to 110 °C under nitrogen for 3 hours, allowed to cool to ambient temperature, and the solvent was removed. The residue was purified by a silica gel chromatography (hexane:ethyl acetate/5:1) to give the title compound as a yellow solid (0.03g, 29%): mp 211-212 °C; ^{1}H-NMR (DMSO-d_6) δ 12.99 (s, 1H), 7.70 (t, 1H, J = 1.7 Hz), 7.64 (m, 1H), 7.58-7.61 (m, 1H), 7.25-7.54 (m, 9H), 5.59 (s, 2H); MS (ESI) *m/z* 349 $[M - H]^-$; Anal. Calc. For $C_{20}H_{15}ClN_2S$: C, 68.46, H, 4.31, N, 7.98. Found: C, 68.07, H, 4.23, N, 7.88.

EXAMPLE 25

1-Benzyl-6-(3-nitrophenyl)-1,3-dihydro-2H-benzimidazole-2-thione

Prepared according to the procedure for Example 24 from 1-benzyl-6-(3-nitrophenyl)-1,3-dihydro-2H-benzimidazole-2-one (0.1g, 0.29 mmol) and Lawesson's reagent (0.13g, 0.32 mmol). A yellow solid (0.025g, 24%): mp 244-245 °C; ^{1}H-NMR (DMSO-d_6) δ 13.08 (s, 1H), 8.43 (s, 1H), 8.20 (dd, 1H, J = 8.2, 1.7 Hz), 8.12 (d, 1H, J = 7.8 Hz), 7.72-7.78 (m, 2H), 7.62 (d, 1H, J = 8.3 Hz), 7.25-7.43 (m, 6H), 5.62 (s,

2H); MS (ESI) *m/z* 360 [M - H]$^-$; Anal. Calc. For $C_{20}H_{15}ClN_2S \cdot 0.2H_2O$: C, 65.81, H, 4.25, N, 11.51. Found: C, 65.56, H, 4.11, N, 11.29.

EXAMPLE 26

6-(3-Nitro-phenyl)-4-methyl-3,4-dihydro-1H-quinoxalin-2-one

Prepared according to the procedure for Example 5 from 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (4.8 g, 20 mmol), and 3-nitrophenylboronic acid (4.8 g, 30 mmol). A red powder (0.95 g, 16 %): mp 237-243 ^{0}C. ^{1}H-NMR (DMSO-d_6) δ 2.88 (s, 3H), 6.9 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 2 Hz, 1H), 7.11 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.7 (t, *J* = 7.9 Hz, 1H), 8.1 (m, 2H), 8.37 (t, *J* = 0.7 Hz), MS (ESI) m/z 283 $(M)^+$

EXAMPLE 27

6-(4-Chloro-phenyl)-3-methyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (22 g, 100mmol), L-alanine (8.9 g, 100 mmol), and potassium carbonate (17.5 g, 125 mmol) in ethanol (250 ml), and water (200 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water, and acidified with 1N hydrochloric acid. The precipitate was collected on a funnel and dried to afford N-(5-bromo-2-nitrophenyl)-alanine (28.9 g, 100%). A sample was recrystallized from ethanol: m.p. 183-187 ^{0}C; ^{1}H-NMR (DMSO -d_6) δ 1.44 (d, *J* = 6.9 Hz, 3H), 4.56 (m, 1H), 6.87 (d, *J* = 6 Hz, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.99 (d, *J* = 7 Hz, 1H), 8.36 (d, *J* = 7 Hz, 1H), 13.27 (s, 1H).

To a solution of N-(5-bromo-2-nitrophenyl)-alanine (22 g, 76 mmol) in acetic acid (300 ml) was added iron powder (10 g, 180 mmol), and the mixture was stirred for 2 hours at 90 ^{0}C. The reaction mixture was cooled and filtered, and the acetic acid was evaporated. The remaining slurry was extracted with methylene chloride (3 x 200 ml). The combined extracts were combined, dried over magnesium sulfate, filtered, and evaporated to afford 6-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (9.4 g, 51 %). A sample was recrystallized from ethanol: m.p. 133-135 ^{0}C. ^{1}H-NMR

(DMSO-d_6) δ 1.23 (d, J = 6.81 Hz, 3H), 3.80 (q, J = 6.81 Hz, 1H), 6.27 (bs, 1H), 6.63 (d, J = 8.35 Hz, 1H), 6.72 (dd, J = 8.35, 1.76 Hz, 1H), 6.80 (d, J = 1.76 Hz, 1H), 10.29 (s, 1H).

A solution of 6-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (2.4 g, 10 mmol), 4-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis-(triphenylphosphine)palladium (0) in dimethoxyethane (150 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature the mixture was diluted with water, and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to obtain crude product (0.83 g, 30 %). A sample was recrystallized from ethanol to afford the title compound: m.p. 228-230 ^{0}C. ^{1}H-NMR (DMSO-d_6) δ 1.28 (d, J = 6.63 Hz, 3H), 3.83 (q, J = 6.63 Hz, 1H), 6.16 (bs, 1H), 6.81 (d, J = 8.00 Hz, 1H), 6.91 (dd, J = 8.05, 1.9 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 10.32 (s, 1H); MS (EI) m/z 272/274.

EXAMPLE 28

4-Benzyl-6-(3-chlorophenyl)-3,4-dihydroquinoxalin-2 (1H)-one

In a manner as described above, 4-bromo-2-fluoro-1-nitro-benzene (11 g, 50 mmol), and N-benzyl-glycine ethyl ester (10 g, 50 mmol) were reacted to give crude [(5-bromo-nitro-phenyl)-benzyl-amino]-acetic acid (10 g, 55 %). This product was reacted with iron powder to obtain crude 4-benzyl-6-bromo-3,4-dihydroquinoxalin-2(1H)-one (5 g, 58 %). A sample was recrystallized from ethyl acetate/hexane: m.p.174-176 ^{0}C. ^{1}H-NMR (DMSO-d_6) δ 3.75 (s, 2H), 4.43 (s, 2H), 6.71 (d, J = 1.9 Hz, 1H), 6.81 (m, 2H), 7.32 (m, 5H), 10.57 (s, 1H).

The title compound was prepared according to the procedure for Example 5 from 4-benzyl-6-bromo-3,4-dihydroquinoxalin-2(1H)-one (1.6 g, 5 mmol), and 3-chlorophenyl boronic acid (0.8 g, 5 mmol). An off-white powder (0.9 g, 51 %): m.p.182-185 ^{0}C ^{1}H-NMR (DMSO-d_6) δ 3.74 (s, 2H), 4.54 (s, 2H), 6.87 (d, J = 0.7

Hz), 7.0 (m, 2H), 7.36 (m, 8H), 7.52 (t, J = 1.8 Hz, 1H), 10.57 (s, 1H), MS (ESI) m/z 349 $(M+H)^+$

EXAMPLE 29

Isopropyl 7-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-carboxylate

To a solution of 7-bromo-3-oxo-3,4-dihydroquinoxaline (6.8 g, 30 mmol) in pyridine (50 ml) was added a solution of isopropyl chloroformate in toluene (35 ml, 1M, 35 mmol) over 30 minutes. The mixture was triturated with water/chloroform, the organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated to obtain crude isopropyl 7-bromo-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate(9.3 g, 97 %). A sample was recrystallized from ethanol: m.p. 159-161 ^{0}C. ^{1}H-NMR (DMSO-d_6) δ 1.25 (d, J = 6.2 Hz, 6H), 4.25 (s, 2H), 4.90 (sep, J = 6.2 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 7.27 (dd, J = 9.1, 2.1 Hz, 1H), 7.74 (s, 1H), 12.51 (s, 1H), MS (ESI) m/z 330/332 $(M+NH_4)^+$.

The title compound was prepared according to the procedure for Example 5 from isopropyl 7-bromo-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate (6.3 g, 20 mmol), and 3-chlorophenyl boronic acid (3.2 g, 20 mmol). Off-white crystals (3.7 g, 49 %): m.p. 174-176 ^{0}C. ^{1}H-NMR (DMSO-d_6) δ 1.27 (d, J = 6.4 Hz, 6H), 4.30 (s, 2H), 4.94 (sep, J = 6.2 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.50 (m, 4H), 7.61 (t, J = 1.9 Hz, 1 H), 7.86 (s, 1H), 10.79 (s, 1H), MS(APCI) m/z 345/347 (M+H)$^+$.

EXAMPLE 30

Isopropyl 7-(3-chlorophenyl)-3-thioxo-3,4-dihydroquinoxaline-1(2H)-carboxylate

Prepared according to the procedure for Example 24 from isopropyl 7-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate and Lawesson's reagent. A yellowish solid: m.p. 208-212 ^{0}C; ^{1}H-NMR (DMSO-d_6) δ 1.27 (d, J = 6.1 Hz, 6H), 4.62 (s, 2H), 4.94 (sep, J = 6.1 Hz, 1H), 7.23 (m, 4H), 7.64 (t, J = 1.8 Hz, 1H), 7.90 (s, 1H), 12.80 (s, 1H), MS (ESI) m/z 359/361 $(M-H)^-$.

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

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